induced a substantial anti-cancer effect *in vitro* and *in vivo*. As a further enhancement the cancer cell killing effect was improved with a tropism modification of the virus to express the knob domain of Ad3, and this improved infectivity for cancer cells. Conversely, the hTERT promoter has low activity in normal tissues, and the CRAd caused no damage to normal lung fibroblast cells. Since the telomerase activity is common in many types of cancers, these CRAds may be applicable to a wide range of tumors. We concluded that the use of hTERT promoter-based CRAds may be a potentially effective strategy for cancer treatment.

965. A Novel Approach for Gene Transduction with Adenovirus/Fibrin Glue System

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Introduction: The major cause of local recurrence after initial surgery for hepatic malignancy is residual carcinoma macroscopically or microscopically at the surgical site. Although many surgical devices and skills have developed, the recurrence rate of hepatic malignancy is still high. At present, for those patients with recurrent disease, adjuvant therapies such as chemotherapy, radiation therapy and immunotherapy are combined. However, in such cases, severe side-effects make the patient's QOL (quality of life) considerably worse. Therefore, a novel approach for residual carcinoma at the time of surgery is urgently needed. In this study we proposed the use of a novel gene therapy for residual carcinoma of the liver. **Purpose:** The fibrin glue system (FGS) consists of liquid forms of fibrinogen and thrombin and is used widely in surgical operation as it has a sealing effect and promotes tissue adhesion at the surgically resected site. In this study, we proposed the efficacy and safety of loco-regional gene transfer using adenoviral vector mixed with FGS to prevent local recurrence of liver carcinoma. We demonstrated that the adenoviral vector containing the E.coli LacZ gene (AxCALacZ) was delivered to the liver of rats by FGS. **Materials and Methods: Experiment 1** ***in vitro*** Rat colon carcinoma cell line, RCN-9 was incubated on a membrane containing multiple 0.02μm-sized holes. Various concentrations of the adenoviral vector mixed with FGS (AxCALacZ/FGS) were applied on the RCN-9 and incubated for 48 hours. The optimum efficiency of transduction was evaluated by X-Gal staining and NIH imaging. **Experiment 2** ***in vitro*** To examine the survival period of adenoviral vector in FGS, AxCALacZ/FGS put on the monolayer cultured RCN9 after being left for various periods. Transgene expression was evaluated by β-gal assay. The β-gal activity was measured photometrically using the Promega β-gal enzyme assay kit according to the manufacture's instructions (Promega, Madison, USA). **Experiment 3** ***in vivo*** 8-week-old male F344 rats underwent a partial hepatectomy. AxCALacZ/FGS was applied on the cut surface of the dissected liver and the rats were kept for 48 hours under normal conditions. AxLacZ/PBS was treated as the control study. The transducted and non-transducted parts of the liver were extirpated, stained with X-gal liquid and β-gal was measured to compare the efficacy of transduction in each organ. **Results: Experiment 1** significantly more transgene expression was shown by the X-gal staining and NIH imaging than 1MOI. **Experiment 2** LacZ expression revealed infected RCN9 when AxCALacZ/FGS was left for a period of less than 96 hours. **Experiment 3** AxCALacZ/FGS transgene expression was shown at the treated and non-treated part of the liver more than AxCALacZ/PBS expression. **Discussion and conclusion:** It was demonstrated that adenoviral vector survives and being stable for enough time to transduct in FGS. AxCALacZ/FGS can transduct the target gene. Furthermore, the transduction efficiency was comparable to those of existing methods. In the future, FGS will be studied with an adenoviral vector containing the gene which enhances antitumor immunity for preventing recurrence loco-regionally site as well as its original tissue adhesive purpose.

966. Synergy between Angiostatin-Endostatin and Tie-2: A Novel Anti-Angiogenic Gene Therapy for Prostate Cancer

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Prostate cancer (CaP) is the most frequently diagnosed cancer in men and the second leading cause of cancer related deaths in American men. In 2003, CaP was expected to account for 220,900 cancer diagnoses and 28,900 cancer deaths. Despite recent advances in the early detection and treatment of locally advanced prostate cancer, the prognosis for patients with the advanced form of prostate cancer is grave. Although a majority of patients with advanced prostate cancer respond initially to androgen ablation therapy, an emergence of the hormone refractory form of the disease, in the absence of continued androgenic stimulation, with widespread metastasis and a fatal outcome is inevitable. Considering the fact that both tumor growth an metastasis are dependent upon angiogenesis, the use of agents that inhibit the generation of new blood vessels represents a potential therapeutic approach for cancer gene therapy. Angiostatin, endostatin and the soluble form of Tie-2 extracellular domain have been shown to be one of the most potent endogenous angiogenesis inhibitors. Since these anti-angiogenic agents operate through different molecular mechanisms, their combination may result in potentially synergistic effects. Towards this goal, we have developed replication defective adenoviral vectors Ad-hEndo-angio, expressing a novel, chimeric endostatin-angiostatin protein and Ad-sTie-2 expressing the soluble form of Tie-2 receptor extracellular domain. We have investigated the anti-angiogenic effects mediated by these vectors either separately or their combination in an androgen independent subcutaneous human PC-3 prostate tumor model following intra-tumoral and systemic delivery. Our in vivo results reveal significant suppression of tumor angiogenesis and inhibition of tumor growth following both intra-tumoral and systemic delivery of Ad-hEndo-angio and Ad-sTie-2 vectors. Further, Ad-hEndo-angio was capable of generating a much more potent anti-angiogenic and anti-tumor effect as compared to Ad-sTie-2. Next we investigated whether a combination of Ad-hEndo-angio and Ad-sTie-2 vectors, each using half the dose following intra-tumoral delivery only in one tumor can inhibit tumor growth and angiogenesis of the tumor on the contralateral side. Our results indicate that this modality resulted in complete tumor eradication on both the sides. These animals have remained tumor free for more than nine months now. Our attempts to challenge these mice with subcutaneous injection of PC-3 cells have failed to generate any tumor during the entire course of the study. To the best of our knowledge, this is the first study of its kind to provide novel insights into the synergistic mode of anti-angiogenic activity in general and will lead to the development of novel anti-angiogenic gene therapy approaches for prostate cancer.